

ANTI-IL-25 ANTIBODIES AND USE THEREOF

FIELD OF THE INVENTION

[0001] The present invention relates to anti-IL-25 antibodies that are directed against (human) IL-25; to nucleic acids that encode such antibodies; to compositions, and in particular pharmaceutical compositions, that comprise such antibodies; and to uses of such antibodies and compositions.

BACKGROUND ART

[0002] IL-25 is a 20 KDa protein mostly known as IL-17E, encoded by chromosome 14, and contains 117 amino acids. Cytokine IL-17 family consists of 6 members; IL-17A to IL-17F, among which IL-25 (i.e., IL-17E) has a unique structure and function (Iwakura Y, et al., *Immunity* 2011; 34: 149-162; Chang S H, Dong C. *Cell Signal* 2011; 23: 1069-1075.). The receptor of IL-25 (IL-17BR) is highly expressed in main Th2 cells (Rouvier E, et al., *J. Immunol.*, 1993; 150:5445-5456). IL-25 regulates internal safety of adaptive immune responses, which leads to begin allergic diseases and plays a role in stimulation of pulmonary mucosal cells and fibroblasts. IL-25 can also have some effects on production of other cytokines. For instance, production of IL-25 in human and mice or injection of IL-25 to animals has resulted in production of high concentrations of Th2 cytokines, including IL-4, IL-5, and IL-13. Pilot studies have shown that mRNA of IL-25 has a high expression in Th2 cells. Groups of researchers have stated that IL-25 is a strong inflammatory cytokine protein which is involved in allergic inflammations (Fort M M, et al., *Immunity* 2001; 15:985-995, Pan G, et al., *J. Immunol.*, 2001; 167:6559-6567; Kim M, et al., *Blood*, 2002; 100: 2330-2340).

[0003] Most allergic diseases result from irregularities in type 2 immune system. Several studies have confirmed that the Th2 cells and mucosal cells, macrophages, eosinophils, basophils, and pulmonary epithelial cells are the hidden producers of IL-25 (Rouvier E, et al. *J. Immunol.*, 1993, 150: 5445-5456). After activation of mammary cells associated with IgE in a mouse model of asthma, a transverse relationship was observed between IL-25 and IgE. According to such findings the highest production was seen 24 h after lung infection in asthma patients. It has been suggested that production of IL-25 by airway macrophages might play a role in regulation of inflammatory responses in lungs. (Wang Y H, et al., *J. Exp Med.* 2007; 204:1837-47).

[0004] Respiratory Syncytial Virus (RSV) increases the risk of progress in asthma among children. Up to now, several studies have been performed on the effects of deficit and decrease in NK cells in the children suffering from RSV. Yet, the important issue is how decrease in the number of NK cells in RSV infection leads to inhibition of INF- α production, progress of Th2, and increase of IL-25, eventually resulting in allergic diseases (Simoes E A, et al., *Lancet.* 1999; 354:847-52). A research conducted by Gerard Aie et al., in 2010 indicated that increase of Th2 reactions and effect of IL-25 derived from respiratory tract epithelial cells enhanced the expression of notch ligand jagged on DC cells, inflammation, and asthma (Gerard E Kaiko, et al., *J Immunol.* 2010; 185:4681-4689).

[0005] Furthermore, in some human studies, sequential single and double immunostaining was used to evaluate the

numbers and phenotypes of IL-25 and IL-25R immunoreactive cells in bronchial biopsies from mild atopic subjects with asthma (n 5 10) before and 24 hours after allergen inhalation challenge and skin biopsies from atopic subjects (n=5-10) up to 72 hours after allergen subepidermal injection. The results showed that IL-25 immunoreactivity was expressed by a majority of epidermal cells in both organs at baseline and was not further augmented by challenge. IL-25R immunoreactive cells were rare in the epidermis before or after challenge. Allergen challenge was associated with significantly ($P<0.01$) increased expression of IL-25 and IL-25R immunoreactivity in the submucosa of both organs. IL-25 immunoreactivity colocalized with eosinophils, mast cells, and endothelial cells, whereas IL-25R immunoreactivity colocalized with eosinophils, mast cells, endothelial cells, and T lymphocytes. In both organs, correlations were observed between increases in IL-25 expression and the magnitudes of the late-phase allergen-induced clinical responses. (Corrigan C J, et al., *J. Allergy Clin Immunol.*, 2011; 128: 117-124).

[0006] During breast cancer development, increased presence of leukocytes in neoplastic stroma parallels disease progression; however, the functional significance of leukocytes in regulating protumor versus antitumor immunity in the breast remains poorly understood. Utilizing the MMTV-PyMT model of mammary carcinogenesis, it has demonstrated that IL-4-expressing CD4+ T lymphocytes indirectly promote invasion and subsequent metastasis of mammary adenocarcinomas by directly regulating the phenotype and effector function of tumor-associated CD11b+Gr1-F4/80+ macrophages that in turn enhance metastasis through activation of epidermal growth factor receptor signaling in malignant mammary epithelial cells. Together, these data indicate that antitumor acquired immune programs can be usurped in protumor microenvironments and instead promote malignancy by engaging cellular components of the innate immune system functionally involved in regulating epithelial cell behavior. (DeNardo D G, et al., *Cancer cell*, 2009, 16: 91-102). Taken together, this cytokine also plays a role in the creation of allergic inflammation in asthma and autoimmune diseases as well as in treatment of cancer.

SUMMARY OF THE INVENTION

[0007] In one aspect, the present invention provides antibodies that are capable of specifically binding to human IL-25, including a murine anti-IL-25 monoclonal antibody 18H3. More particular, the invention relates to antibodies that (i) competes with murine antibody 18H3 for binding to (human) IL-25; and/or (ii) binds to the same epitope on (human) IL-25 as 18H3; and/or (iii) cross-blocks the binding of 18H3 to (human) IL-25.

[0008] In another aspect, the present invention provides an isolated nucleic acid encoding the antibody according to the invention.

[0009] In a further aspect, the present invention provides host cell comprising the nucleic acid as recited above.

[0010] In a still further aspect, the present invention provides a method of producing the antibody according to the invention comprising culturing the host cell as recited above so that the antibody is produced.

[0011] In another aspect, the present invention also provides a pharmaceutical composition comprising the antibody according to the invention and a pharmaceutically acceptable carrier.